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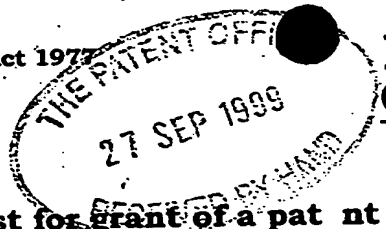

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2.	Patent application number *(The Patent Office will fill in this par.*	9922830.6 27 SEP 1999
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG SCHWARZWALDALLEE 215 4058 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7125487002
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Processes
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

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11. I/We request the grant of a patent on the basis of this application

Signature: B A Yorke & Co

B.A. Yorke & Co.

Date: **27.09.99**

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. E. Cheetham

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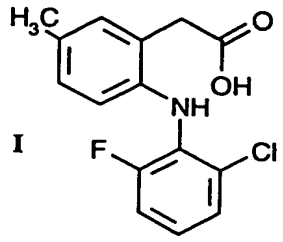
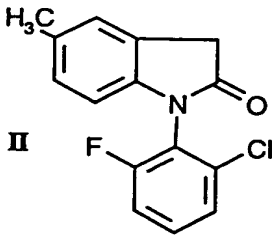
PROCESSES

The present invention relates to processes for the production of [2-(2'-chloro-6'-fluoro-phenylamino)-5-methyl-phenyl]acetic acid (the compound of formula I given below), intermediates therefor and pharmaceutically acceptable salts thereof and pharmaceutically acceptable prodrug esters thereof.



I

Accordingly the invention provides a process for the production of a compound of Formula I, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable and physiologically cleavable prodrug ester thereof, comprising hydrolysing an oxindole lactam of formula II



II

with a base; and in the above process, if desired, temporarily protecting any interfering reactive groups and then isolating the resulting compound of the invention; and, if desired, converting the free carboxylic acid of the compound of formula I into a pharmaceutically acceptable ester derivative thereof; and/or if desired, converting the free acid of formula I into a salt or a resulting salt into the free acid or into another salt.

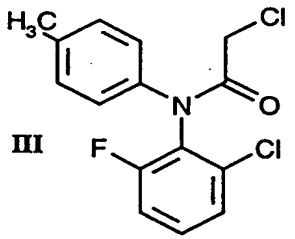
The above process may be carried out under conditions known in the art for the hydrolytic cleavage of lactams, preferably with a strong base, such as aqueous sodium hydroxide (e.g. a 30% aqueous solution of NaOH), optionally in the presence of a water miscible organic solvent such as ethanol or methanol, preferably at elevated temperature, e.g. at a temperature in the range from about 50° to 100°C, (for instance

as generally described in US Patent 3,558,690). The resultant reaction mixture is conveniently neutralised with an acid, e.g. a mineral acid such as hydrochloric acid to give the free acid product of formula I, which may be recovered by crystallisation, e.g. on cooling of the reaction mixture to ambient temperature, and filtration.

Pharmaceutically acceptable prodrug esters are ester derivatives which are convertible by solvolysis or under physiological conditions to the free carboxylic acids of formula I. Such esters are e.g. lower alkyl esters (such as the methyl or ethyl ester), carboxy-lower alkyl esters such as the carboxymethyl ester, nitrooxy-lower alkyl esters (such as the 4-nitrooxybutyl ester), and the like.

Pharmaceutically acceptable salts represent metal salts, such as alkaline metal salts, e.g. sodium, potassium, magnesium or calcium salts, as well as ammonium salts, which are formed e.g. with ammonia and mono- or di-alkylamines, such as diethylammonium salts, and with amino acids such as arginine and histidine salts.

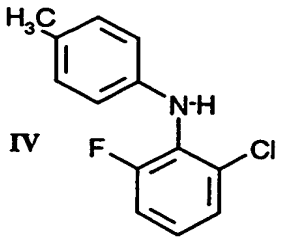
The oxindole lactam of formula II is obtained by cyclisation of a compound of formula III



III

The cyclisation process is conveniently carried out under Friedel-Crafts alkylation conditions, e.g. in the presence of a Friedel-Crafts catalyst such as aluminium chloride or ethyl aluminium dichloride, preferably at elevated, e.g. a temperature in the range from about 100° to about 180°C. The cyclisation reaction may be carried out in the presence of an inert solvent such as dichlorobenzene, or preferably a melt of the compound of formula III is heated with the Friedel-Crafts catalyst.

The compound of formula III is prepared by N-acylation of a diphenylamine of formula IV (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine)

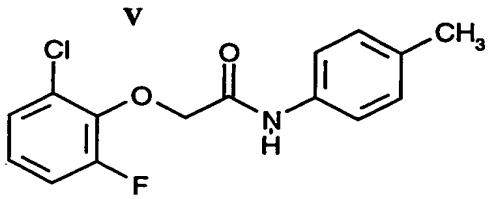


IV

with a haloacetyl chloride.

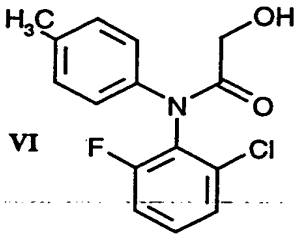
For instance, the compound of formula IV is heated, e.g. to about 80°C, with chloroacetylchloride. The product may be recovered by diluting the reaction mixture with solvent, e.g. 2-propanol, and crystallisation.

The compound of formula IV may be obtained by rearrangement and hydrolysis of a compound of formula V.



V

Conveniently the compound of formula V is treated with an organic base, e.g. an alkali metal alkoxide such as sodium methoxide, preferably with heating, e.g. to a temperature of at least about 75°C. During this procedure an intermediate product of formula VI



VI

forms as a result of the initial rarrangement reaction, but undergoes direct hydrolysis under the prevailing reaction conditions to give the diphenylamine compound of formula IV.

Alternatively the diphenylamine compound of formula IV may be obtained by coupling of 2-bromo-1-chloro-3-fluorobenzene with p-toluidine. Such a coupling reaction may be carried out by use of Buchwald chemistry. For example, the 2-bromo-1-chloro-3-fluorobenzene and the p-toluidine are mixed with an organic base, e.g. sodium tertiary butylate, and an appropriate ligand, e.g. BINAP, in an organic solvent

such as toluene; a palladium compound or catalyst precursor such as $Pd(dba)_2$ is added and the reaction mixture is heated. after cooling and treatment with acid, e.g. HCl, the diphenylamine product of formula IV may be recovered from the organic phase of the reaction mixture.

In a further alternative the diphenylamine compound of formula IV may be obtained by coupling of 2-chloro-6-fluoroaniline with 4-bromotoluene. Such a coupling reaction may be carried out similarly by use of Buchwald chemistry. For example, the 2-chloro-6-fluoroaniline and 4-bromotoluene are mixed with an organic base, e.g. sodium tertiary butylate in an organic solvent such as toluene; a palladium compound or catalyst precursor e.g. $Pd(dba)_2$, and a ligand, e.g. $P(tBu)_3$, or BINAP, are added to this reaction mixture which is then stirred at elevated temperature, e.g. 110°C, until completion of the reaction, e.g. overnight. Similarly the diphenylamine product of formula IV may be recovered from the organic phase of the reaction mixture, for instance after cooling and treatment with acid, e.g. HCl.

The compound of formula V is prepared by alkylation of 2-chloro-6-fluorophenol with 2-chloro-N-(4-methylphenyl)acetamide. For instance, 2-chloro-6-fluorophenol and 2-chloro-N-(4-methylphenyl)acetamide are mixed in an organic solvent such as 2-propanol in the presence of a base, e.g. K_2CO_3, and the reaction mixture boiled until completion of the reaction, e.g. for about 4 hours. The compound of formula V may be recovered from the reaction mixture if desired. Preferably, however, the compound of formula V is not isolated but is converted to the compound of formula IV, by rearrangement and hydrolysis as described above carried out on the product reaction mixture resulting from the alkylation of 2-chloro-6-fluorophenol with 2-chloro-N-(4-methylphenyl) acetamide.

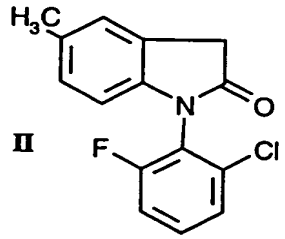
In starting compounds and intermediates, which are converted to the compounds of formulae I to VI in a manner as hereinbefore described, functional groups present such as amino, hydroxy and carboxyl groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected hydroxy, amino and carboxyl groups are those that can be converted under mild conditions into free amino, hydroxy and carboxyl groups without other

undesirable side reactions taking place. For example, hydroxy protecting groups are preferably benzyl or substituted benzyl groups.

The processes for the production of the compounds of formulae II, III, IV, V and VI, as described above, are novel processes and are included within the scope of the present invention.

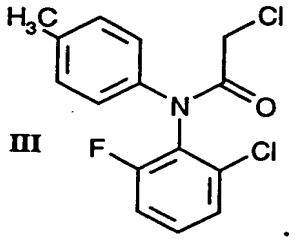
~~Thus in further aspects the invention includes~~

a) a process for the production of the oxindole lactam of formula II



II

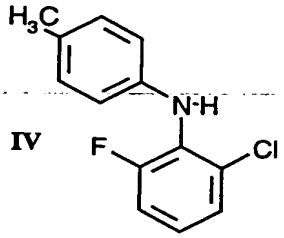
which comprises cyclisation of a compound of formula III



III

;

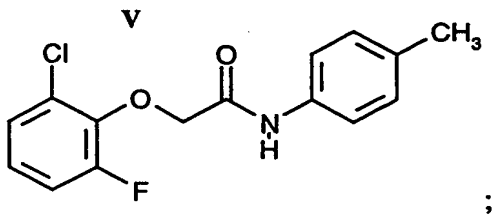
b) a process for the production of a compound of formula III which comprises N-acylation of a diphenylamine of formula IV (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine



IV

with a haloacetyl chloride;

c) a process for the preparation of a compound of formula IV which comprises rearrangement and hydrolysis of a compound of formula V.

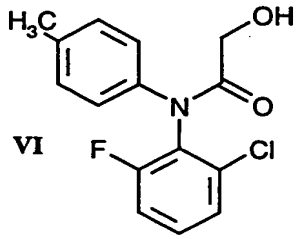
V 

;

d) a process for the production of a compound of formula IV which comprises coupling of 2-bromo-1-chloro-3-fluorobenzene with p-toluidine;

e) a process for the production of a compound of formula IV which comprises coupling of 2-chloro-6-fluoroaniline with 4-bromotoluene;

f) a process for the production of a compound of formula IV which comprises hydrolysis of a compound of formula VI



VI

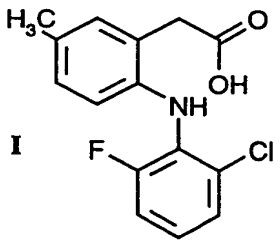
g) a process for the formation of a compound of formula VI which comprises rearrangement of a compound of formula V;

h) a process for the production of a compound of formula V which comprises alkylation of 2-chloro-6-fluorophenol with 2-chloro-N-(4-methylphenyl)acetamide; and

i) a process for the production of a compound of formula IV which comprises alkylation of 2-chloro-6-fluorophenol with 2-chloro-N-(4-methylphenyl)acetamide followed by rearrangement and hydrolysis of the intermediate compound of formula V.

One or more of the processes a) to i) above may be used in the preparation of the compound of formula I.

Thus the invention further provides a process for the preparation of a compound of formula I



I

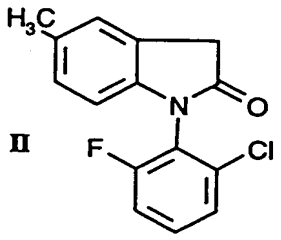
which comprises one or more of processes a) to i) as defined above.

Still yet further the invention provides a compound of formula I, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable prodrug ester thereof, when prepared by a process which comprises one or more of processes a) to i) as defined above.

The compounds of formulae II, III, IV, V and VI are novel compounds and are included per se within the scope of the present invention.

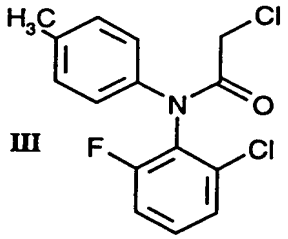
Thus in yet further aspects the invention provides:

a) a compound of formula II



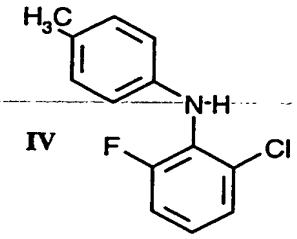
II

b) a compound of formula III



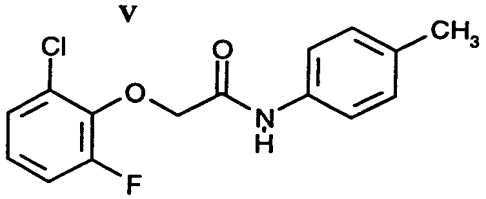
III

c) a compound of formula IV



IV

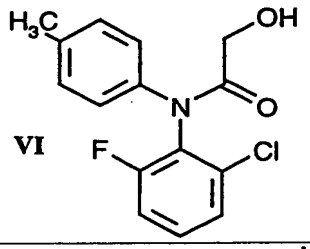
d) a compound of formula V



V

and

e) a compound of formula VI



VI

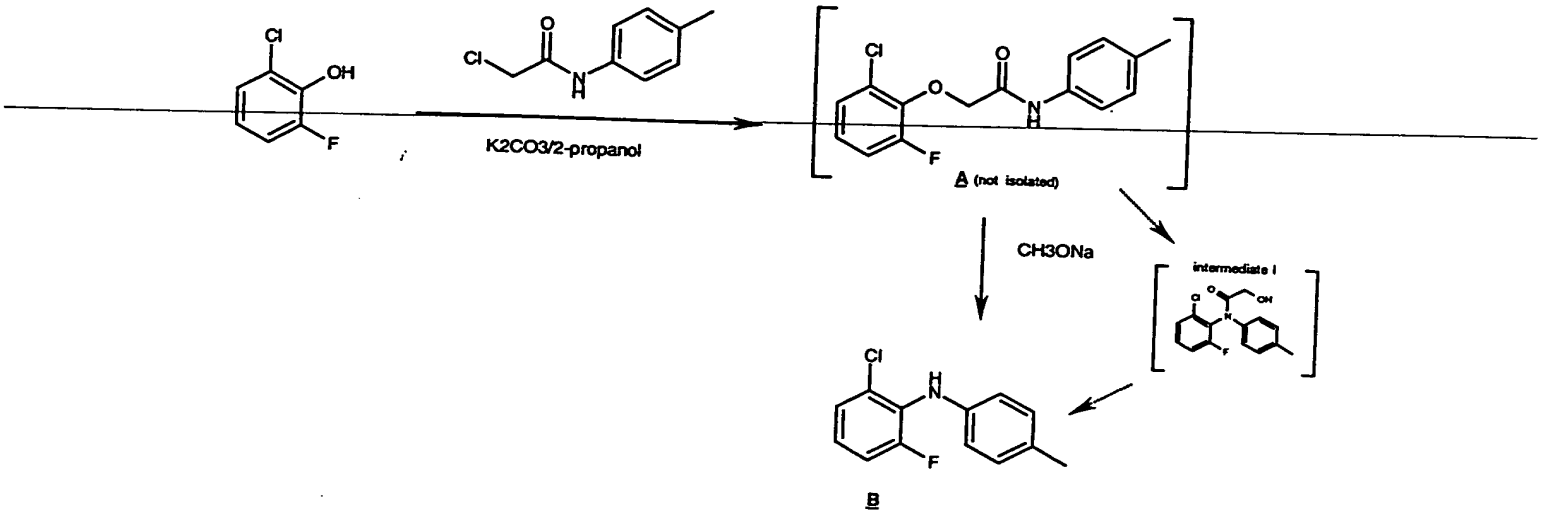
2-chloro-6-fluorophenol may be prepared by chlorination of 2-fluorophenol, preferably in the presence of catalytic amounts of a secondary amine, e.g. diisopropylamine. In a preferred embodiment according to the present invention, the chlorination reaction comprises simultaneous addition of chlorine and 2-fluorophenol to the reaction mixture, preferably using hexane fraction as the solvent. It has been found that simultaneous addition of at least part, preferably the majority, of the chlorine and 2-fluorophenol to the reaction mixture gives rise to high productivity and selectivity in production of the desired 2-chloro-6-fluorophenol product as compared with the unwanted 4-chloro and 2,4-dichloro side products. Furthermore use of hexane fractions permits isolation of the desired 2-chloro-6-fluorophenol product in high purity (e.g. 99%) by crystallisation.

Thus in a further aspect the invention provides a process for the production of 2-chloro-6-fluorophenol by chlorinationof 2-fluorophenol, which comprises simultaneous addition of chlorine and 2-fluorophenol to the reaction mixture, preferably using a solvent comprising hexane fraction.

The invention is further described by way of illustration only in the following Examples.

EXAMPLES

Example 1: **(2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine**



14.65 g (100 mmol) of 2-chloro-6-fluorophenol are dissolved in 50 ml of 2-propanol followed by the addition of 15.5 g (112 mmol) of potassium carbonate and 18.9 g (103 mmol) of 2-chloro-N-(4-methylphenyl)acetamide. The mixture is refluxed for 4h. At this time, the formation of A : 2-(2'-chloro-6'-fluorophenoxy)-N-(4-methylphenyl)acetamide is completed.

20 ml of sodium methylate solution 30% in methanol are slowly added. To maintain a temperature of at least 75°C, about 25 ml of solvent are distilled during the addition. The mixture is boiled 2h more to complete the formation of B.

Then 15 ml of solvent is distilled and 35 ml of water is added to obtain a two phases solution. The lower layer is discarded. The upper layer is diluted with 35 ml of heptane and washed with 3x 25 ml of water. The organic phase is separated and concentrated in vacuo to obtain 21.8 g of crude oil B: (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine. This compound (HPLC purity 92%) is used without purification in the next step.

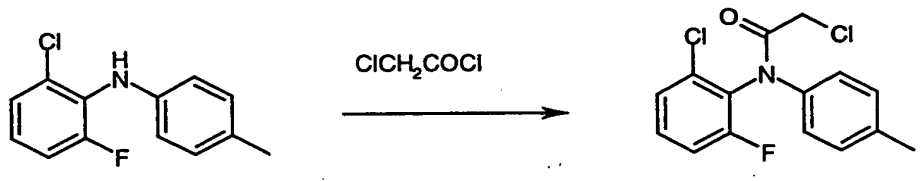
^{1}H-NMR (DMSO-d^6, 500 MHz, 300K) δ 2.17(s, 3H, CH_3); 6.53[dd, J = 8.5Hz, $J_{H\text{-}F}$ = 1.5, 2H, HC(2) and HC(6)], 6.94[d, J = 8.0Hz, 2H, HC(3) and HC(5)],

7.16[ddd, J = 8.0Hz, J_{H-F} = 6.0, 1H, HC(4')], 7.25[ddd, J = 8.0,1.5Hz, J_{H-F} = 8.0, 1H, HC(5')]; 7.34[ddd, J = 8.0,1.5Hz, J_{H-F} = 1.5, 1H, HC(3')]; 7.63(s, 1H, NH).

MS(EI) m/z 235 (100, M^+), 200 (35, $(M-Cl)^+$), 185 (55)

Example 2.

2-chloro-N-(2'-chloro-6'-fluorophenyl)-N-(4-methylphenyl) acetamide



20.4 g of crude (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine are heated to about 80°C and treated with 10.75 g of chloroacetylchloride. The mixture is stirred for 2h and diluted with 10 ml of 2-propanol. The solution is cooled to 35-40°C and seeded. The precipitated suspension is diluted with 30 ml of hexane, cooled to 0-5°C and stirred for about 1h. The crystals are isolated by filtration, washed with a cold solution of 2-propanol/hexane 1/3. After drying, 22.7 g of 2-chloro-N-(2'-chloro-6'-fluorophenyl)-N-(4-methylphenyl)acetamide are obtained. HPLC purity: 99%. M.P.: 79-80°C.

^{1}H-NMR(DMF-d^7, 400 MHz, 393K) δ 2.44(s, 3H, CH_3); 4.32 (s, 2H, CH_2), 7.35[d, J = 8.0Hz, 2H, HC(3) and HC(5)], 7.43[ddd, J = 8.0,2.0Hz, J_{H-F} = 8.0 , 1H, HC(5')], 7.48[d, J = 8.0Hz, 2H, HC(2) and HC(6)], 7.55[d, J = 8.0Hz, 1H, HC(3')], 7.60[ddd, J = 8.0Hz, J_{H-F} = 5.5, 1H, HC(4')].

Preparation of starting material 2-chloro-6-fluorophenol

A solution of 12.1 g (108 mmol) of 2-fluorophenol, 70 mg of diisopropylamine and 400 ml of hexane-fraction is heated to 60-65°C.

4 g (56 mmol) of chlorine is introduced at this temperature. Then 60.5 g (540 mmol) of 2-fluorophenol are dropped in the solution over about 2h, while at the same rate 42g

(590 mmol) more chlorine is introduced. After that 4 g more chlorine are introduced to complete the chlorination.

GC check: 91% of 2-chloro-6-fluorophenol.

5.2% of 4-chloro-6-fluorophenol

3.5% of 2,4-dichloro-6-fluorophenol

200-250 ml of solvent are distilled at normal pressure. The resulting concentrated solution is slowly cooled to 0-5°C. The obtained thick suspension is stirred at this temperature for 1h, washed with cold hexane-fraction and dried at room temperature.

Yield: 78 g white crystals. GC 99.7%. M.P.: 63.5-64.5°C

MS(EI) m/z 146 (100, M^+), 126 [19, $(M-HF)^+$]

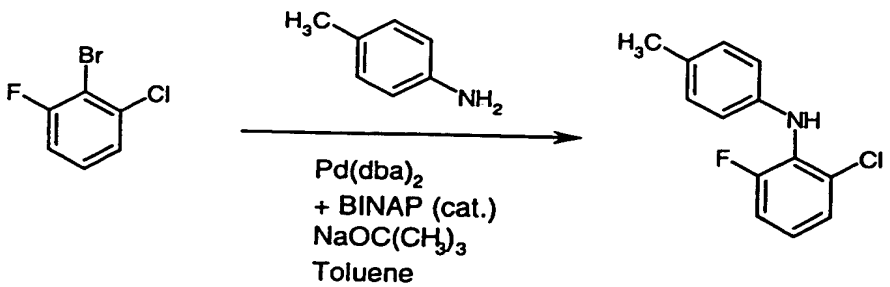
^{1}H-NMR(DMSO-d^6, 500MHz, 300K) δ 6.8[ddd, J = 8.2 Hz, J_{H-F} = 5.5, 1H, HC(4)], 7.15[m, 2H, HC(3) and HC(5)], 10.3(s, 1H, OH).

Preparation of starting material 2-chloro-N-(4-methylphenyl)acetamide

To a stirred mixture of 34.5 g (322 mmol) of p-toluidine, 100 ml of toluene and 100 ml of water are added at 20-25°C from two separated dropping funnels 42.3 g (375 mmol) of chloroacetylchloride and 39 ml of concentrated sodium hydroxide 30% at such a rate to maintain a pH of 8-12. The obtained suspension is cooled to 0-5°C. The crystalline compound is filtered, washed with water and cold toluene and dried.

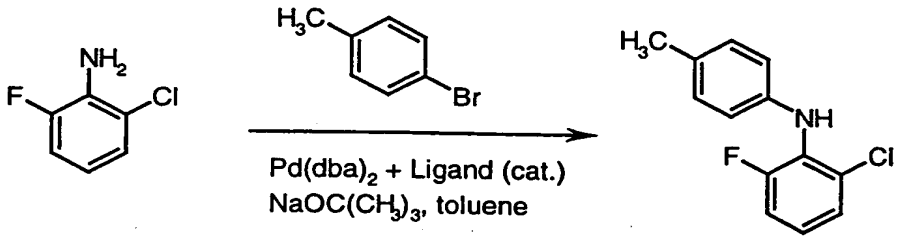
Yield: 55 g HPLC > 99%.

Example 3: (2'-Chloro-6'-fluorophenyl)-(4-methylphenyl)-amine from 2-bromo-1-chloro-3-fluorobenzene and p-toluidine.



A mixture of 2-bromo-1-chloro-3-fluorobenzene (32 g, 153 mmol), p-toluidine (16.4 g, 153 mmol), sodium tert.butylate (27.5 g, 286 mmol), (±)-BINAP [2,2'-Bis-(diphenylphosphino)-1,1'-binaphthalin, 0.66g, 1.1 mmol) and toluene (250 ml) is stirred under nitrogen for about 30 minutes. After the addition of Palladium-bis-(dibenzylidenaceton) (0.8 g, 1 mmol), the mixture is heated to 110°C (slight reflux) for 14-20 hours. The mixture is then cooled to 30°C, water (60 ml), concentrated hydrochloric acid (60 ml) as well as charcoal and cellite (5 g each) are added and stirring is continued for an hour. The mixture is filtered and the filtrate is separated into the phases. The organic phase is washed with water (3 times, 70 ml each) and concentrated in vacuo to obtain 37.2 g of crude (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine. The product can be used in the next step as such; alternatively in can be kugelrohrdistilled in vacuo.

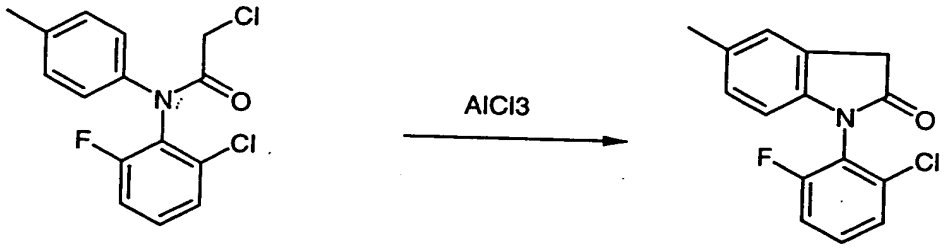
Example 4: **(2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine from 2-chloro-6-fluoroaniline and 4-bromotoluene.**



A mixture of 2-chloro-6-fluoroaniline (4.00g, 27.5 mmol), 4-bromotoluene (4.70 g, 27.5 mmol), sodium *tert*-butylate (4.75 g, 49.4 mmol), and toluene (55 mL) is stirred at 25 °C under nitrogen for 30 minutes. To this mixture, a solution of palladium-bis-(dibenzylidenacetone) (15.8 mg, 55 mmol) and tri-*tert*-butylphosphine (1) (8.3 mg, 0.04 mmol) in toluene (5 mL) is added and the resulting suspension. is stirred at 110°C for 14 hours. The mixture is then cooled to 30°C. Water (30 ml), concentrated hydrochloric acid (10 ml), charcoal and cellite (1 g each) are added and stirring is continued for 1 hour. The mixture is filtered and the filtrate is separated into its phases. The organic phase is washed three times with water (10 mL) and

concentrated *in vacuo* to give 6.5 g of crude (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine. The product can be used directly in the next step. Alternatively, it can be distilled *in vacuo* by Kugelrohr.

Example 5: 1-(2'-Chloro-6'-fluorophenyl)-5-methyl-1,3-dihydro-indol-2-one

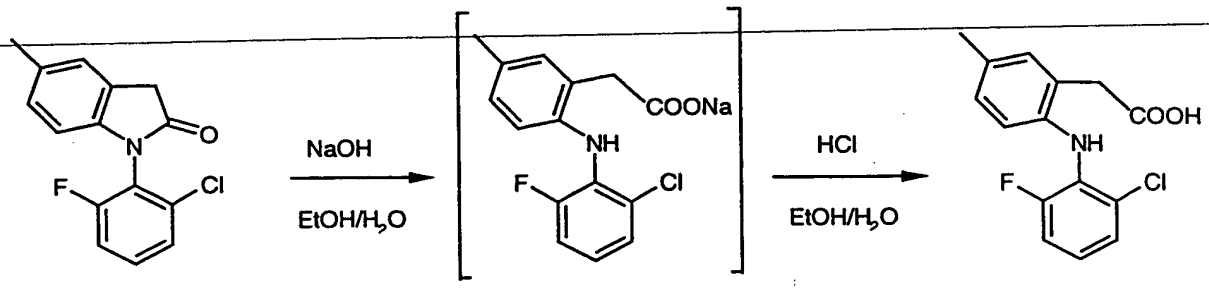


A melt of 124.8 g (400 mmol) of 2-chloro-N-(2'-chloro-6'-fluorophenyl)-N-(4-methylphenyl)acetamide at 100-120°C is treated with 69.3 g (520 mmol) of aluminium chloride in small parts. The mixture is heated to 160°C and stirred for 4-6h at this temperature.

The molten mixture is cooled to 110°C and diluted with 300 ml of toluene. The obtained solution is added to 500 ml of water at 60°C. The organic phase is separated while hot, decolorized with activated carbon, filtered and concentrated. The residue is dissolved in hot 2-propanol, decolorized again with activated carbon, filtered and concentrated to a volume of about 250 ml. The obtained suspension is cooled to 0-5°C, filtered, washed with cold 2-propanol. After drying, 87 g of 1-(2'-chloro-6'-fluorophenyl)-5-methyl-1,3-dihydro-indol-2-one are obtained. M.P.: 137.5-138.5°C

^{1}H-NMR(DMSO-d^6, 500 MHz, 300K) δ 2.27(s, 3H, CH_3); 3.83(s, 2H, CH_2); 6.35[d, J = 8.0Hz, 1H, HC(7)], 7.01[d, J = 8.0Hz, 1H, HC(6)], 7.19[s, 1H, CH(4)], 7.52[ddd, J = 8.5,2.0Hz, J_{H-F} = 10.0, 1H, HC(5')], 7.60[ddd, J = 8.5,2.0Hz, J_{H-F} = 1.5, 1H, HC(3')], 7.63[ddd, J = 8.5Hz, J_{H-F} = 1.5, 1H, HC(4')].

Example 6. **[2-(2'-chloro-6'-fluoro-phenylamino)-5-methyl-phenyl]acetic acid**

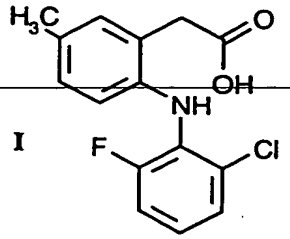


A mixture of 20 g of 1-(2'-chloro-6'-fluorophenyl)-5-methyl-1,3-dihydro-indol-2-one, 266 ml of ethanol and 11 ml of water is heated to reflux. 24 g of a 30% solution of sodium hydroxide is slowly added and reflux is continued for 1h. The solution is cooled to 40-45°C and treated slowly with a solution of 18 g of concentrated hydrochloric acid in 94 g of deionized water up to a pH of 3-4. The obtained suspension is cooled to 20-25°C and the crystalline material is collected by filtration, washed with ethanol/deionized water and dried under reduced pressure to yield 19.5 g of pure [2-(2'-chloro-6'-fluoro-phenylamino)-5-methyl-phenyl]acetic acid. M.P.: 152-154°C

^{1}H-NMR(DMSO-d^6, 500MHz, 300K) δ 2.21(s, 3H, CH_3), 3.64(s, 2H, CH_2); 6.42[dd, J = 8.0Hz, J_{H-F} = 3.0, 1H, HC(6)], 6.90[dd, J = 8.0,2.0Hz, 1H, HC(5)], 7.01[d, J = 2.0Hz, 1H, HC(3)], 7.09(s, 1H, NH), 7.09[ddd, J = 8.5Hz, J_{H-F} = 5.5, 1H, HC(4')], 7.23[ddd, J = 8.5,1.5Hz, J_{H-F} = 11.0, 1H, HC(5')], 7.34[ddd, J = 8.5,1.5Hz, J_{H-F} = 1.5, 1H, HC(3')], 12.67(s, 1H, COOH).

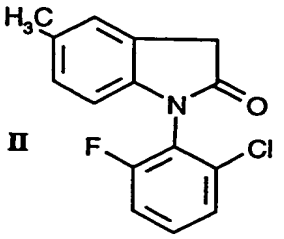
CLAIMS

1. process for the production of a compound of Formula I, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable prodrug ester thereof,



I

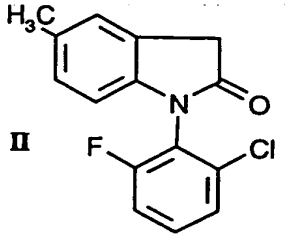
comprising hydrolysing a lactam of formula II



II

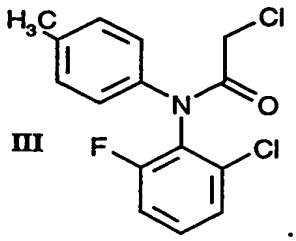
with a base; and in the above process, if desired, temporarily protecting any interfering reactive groups and then isolating the resulting compound of the invention; and, if desired, converting the free carboxylic acid of the compound of formula I into a pharmaceutically acceptable ester derivative thereof; and/or if desired, converting the free acid of formula I into a salt or a resulting salt into the free acid or into another salt.

2. a) a process for the production of the oxindole lactam of formula II



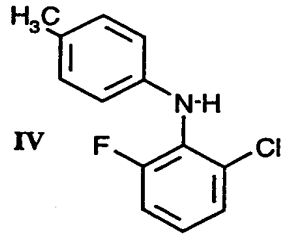
II

which comprises cyclisation of a compound of formula III

III 

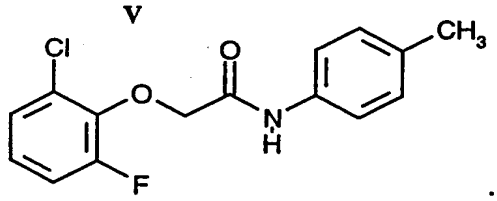
;

b) a process for the production of a compound of formula III which comprises N-acylation of a diphenylamine of formula IV (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine)

IV 

with a haloacetyl chloride;

c) a process for the preparation of a compound of formula IV which comprises rearrangement and hydrolysis of a compound of formula V.

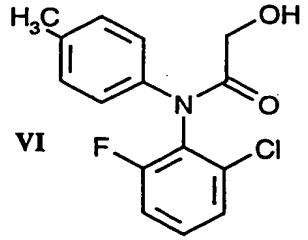
V 

;

d) a process for the production of a compound of formula IV which comprises coupling of 2-bromo-1-chloro-3-fluorobenzene with p-toluidine;

e) a process for the production of a compound of formula IV which comprises coupling of 2-chloro-6-fluoroaniline with 4-bromotoluene;

f) a process for the production of a compound of formula IV which comprises hydrolysis of a compound of formula VI



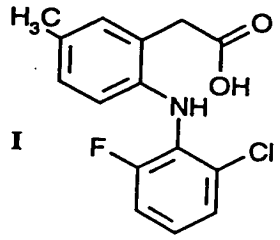
g) a process for the formation of a compound of formula VI

which comprises rearrangement of a compound of formula V;

h) a process for the production of a compound of formula V which comprises alkylation of 2-chloro-6-fluorophenol with 2-chloro-N-(4-methylphenyl)acetamide; or

i) a process for the production of a compound of formula IV which comprises alkylation of 2-chloro-6-fluorophenol with 2-chloro-N-(4-methylphenyl)acetamide followed by rearrangement and hydrolysis of the intermediate compound of formula V.

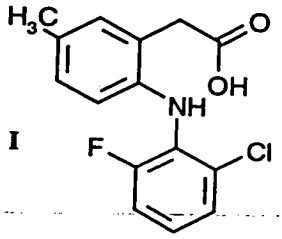
3. A process for the preparation of a compound of formula I



I

which comprises one or more of processes a) to i) as defined in claim 2.

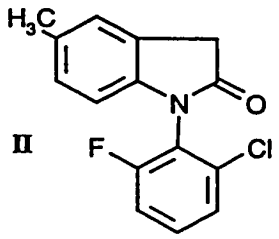
4. A compound of formula I,



I

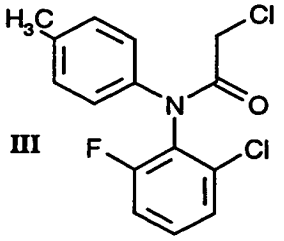
or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable prodrug ester thereof, when prepared by a process which comprises one or more of processes a) to i) as defined in claim 2.

5. a) a compound of formula II



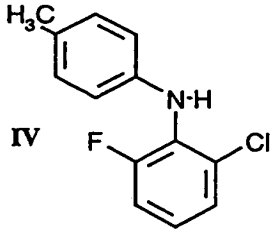
II

b) a compound of formula III



III

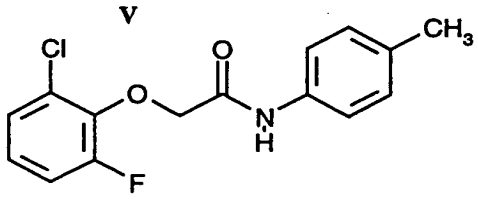
c) a compound of formula IV



IV

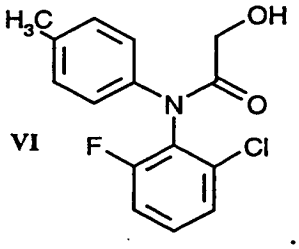
d) a compound of formula V

V



or

e) a compound of formula VI



VI

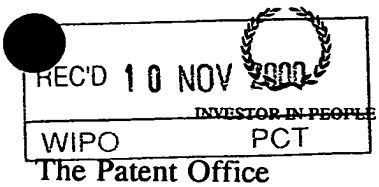
6. A process for the production of 2-chloro-6-fluorophenol by chlorination of 2-fluorophenol, which comprises simultaneous addition of chlorine and 2-

fluorophenol to the reaction mixture, preferably using a solvent comprising hexane fraction.

7. All novel products processes and utilities substantially as hereinbefore described, particularly with reference to the examples.

PCT/EP 00/09346

EP00/09346



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The Patent Office
Concept House
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Newport
South Wales
NP10 8QQ

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10/089038

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

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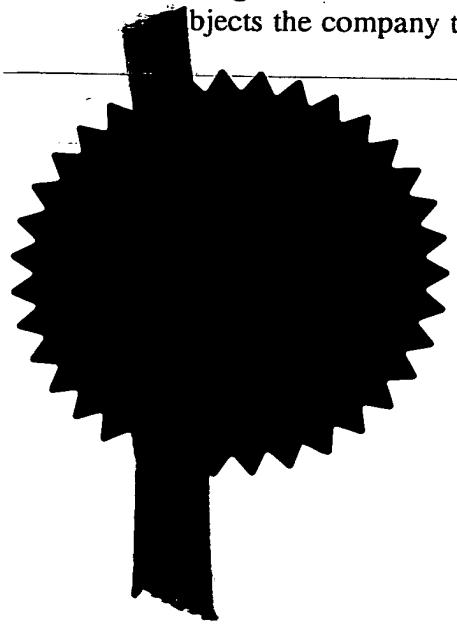
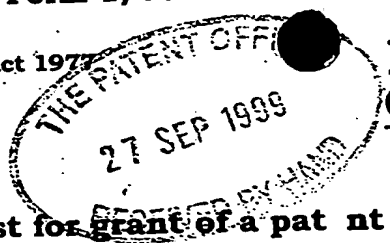


Signed R. Mahoney

Dated 14 August 2000

Patents Form 1/77

Patents Act 1977
(Rule 16)



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1/77

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P01/7700 0.00 - 9922830.6

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1.	Your reference	4-31153P1
2.	Patent application number *(The Patent Office will fill in this part)*	9922830.6 27 SEP 1999
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG SCHWARZWALDALLEE 215 4058 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	7125487002
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Processes
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH
	Patents ADP number *(if you know it)*	1800001

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

   a) any applicant named in part 3 is not an inventor, or

   b) there is an inventor who is not named as an applicant, or

   c) any named applicant is a corporate body.

   (see note (d))

   Yes

Pat nts Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	**14**
Claim(s)	**5**
Abstract	
~~Drawing(s)~~	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	**One**
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B A. Yorke & Co. — **B.A. Yorke & Co.**

Date: **27.09.99**

12. Name and daytime telephone number of person to contact in the United Kingdom: **Mrs. E. Cheetham** **020 8560 5847**

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Notes

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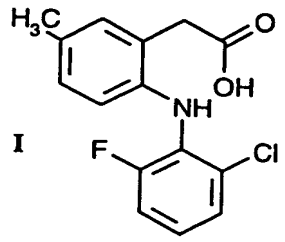
d) Once you have filled in the form you must remember to sign and date it.

e) For details of the fee and ways to pay please contact the Patent Office.

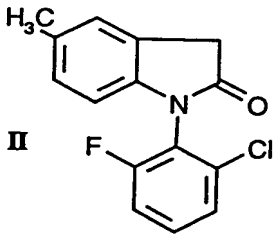
PROCESSES

The present invention relates to processes for the production of [2-(2'-chloro-6'-fluoro-phenylamino)-5-methyl-phenyl]acetic acid (the compound of formula I given below), intermediates therefor and pharmaceutically acceptable salts thereof and pharmaceutically acceptable prodrug esters thereof.



I

Accordingly the invention provides a process for the production of a compound of Formula I, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable and physiologically cleavable prodrug ester thereof, comprising hydrolysing an oxindole lactam of formula II



II

with a base; and in the above process, if desired, temporarily protecting any interfering reactive groups and then isolating the resulting compound of the invention; and, if desired, converting the free carboxylic acid of the compound of formula I into a pharmaceutically acceptable ester derivative thereof; and/or if desired, converting the free acid of formula I into a salt or a resulting salt into the free acid or into another salt.

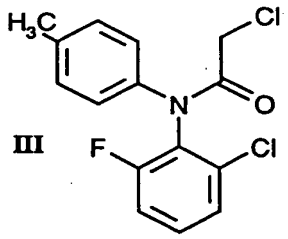
The above process may be carried out under conditions known in the art for the hydrolytic cleavage of lactams, preferably with a strong base, such as aqueous sodium hydroxide (e.g. a 30% aqueous solution of NaOH), optionally in the presence of a water miscible organic solvent such as ethanol or methanol, preferably at elevated temperature, e.g. at a temperature in the range from about 50° to 100°C, (for instance

as generally described in US Patent 3,558,690). The resultant reaction mixture is conveniently neutralised with an acid, e.g. a mineral acid such as hydrochloric acid to give the free acid product of formula I, which may be recovered by crystallisation, e.g. on cooling of the reaction mixture to ambient temperature, and filtration.

Pharmaceutically acceptable prodrug esters are ester derivatives which are convertible by solvolysis or under physiological conditions to the free carboxylic acids of formula I. Such esters are e.g. lower alkyl esters (such as the methyl or ethyl ester), carboxy-lower alkyl esters such as the carboxymethyl ester, nitrooxy-lower alkyl esters (such as the 4-nitrooxybutyl ester), and the like.

Pharmaceutically acceptable salts represent metal salts, such as alkaline metal salts, e.g. sodium, potassium, magnesium or calcium salts, as well as ammonium salts, which are formed e.g. with ammonia and mono- or di-alkylamines, such as diethylammonium salts, and with amino acids such as arginine and histidine salts.

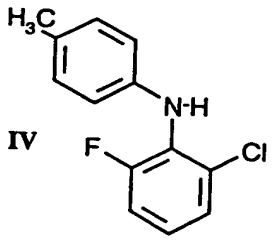
The oxindole lactam of formula II is obtained by cyclisation of a compound of formula III



III

The cyclisation process is conveniently carried out under Friedel-Crafts alkylation conditions, e.g. in the presence of a Friedel-Crafts catalyst such as aluminium chloride or ethyl aluminium dichloride, preferably at elevated, e.g. a temperature in the range from about 100° to about 180°C. The cyclisation reaction may be carried out in the presence of an inert solvent such as dichlorobenzene, or preferably a melt of the compound of formula III is heated with the Friedel-Crafts catalyst.

The compound of formula III is prepared by N-acylation of a diphenylamine of formula IV (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine)

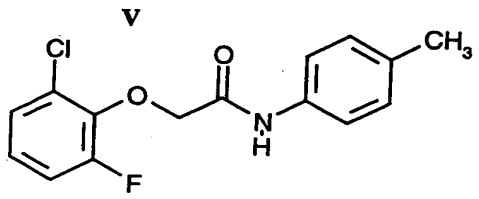


IV

with a haloacetyl chloride.

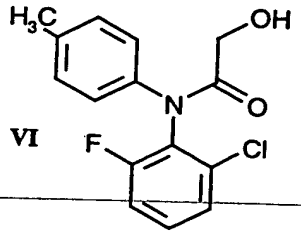
For instance, the compound of formula IV is heated, e.g. to about 80°C, with chloroacetylchloride. The product may be recovered by diluting the reaction mixture with solvent, e.g. 2-propanol, and crystallisation.

The compound of formula IV may be obtained by rearrangement and hydrolysis of a compound of formula V.



V

Conveniently the compound of formula V is treated with an organic base, e.g. an alkali metal alkoxide such as sodium methoxide, preferably with heating, e.g. to a temperature of at least about 75°C. During this procedure an intermediate product of formula VI



VI

forms as a result of the initial rarrangement reaction, but undergoes direct hydrolysis under the prevailing reaction conditions to give the diphenylamine compound of formula IV.

Alternatively the diphenylamine compound of formula IV may be obtained by coupling of 2-bromo-1-chloro-3-fluorobenzene with p-toluidine. Such a coupling reaction may be carried out by use of Buchwald chemistry. For example, the 2-bromo-1-chloro-3-fluorobenzene and the p-toluidine are mixed with an organic base, e.g. sodium tertiary butylate, and an appropriate ligand, e.g. BINAP, in an organic solvent

such as toluene; a palladium compound or catalyst precursor such as $Pd(dba)_2$ is added and the reaction mixture is heated. after cooling and treatment with acid, e.g. HCl, the diphenylamine product of formula IV may be recovered from the organic phase of the reaction mixture.

In a further alternative the diphenylamine compound of formula IV may be obtained by coupling of 2-chloro-6-fluoroaniline with 4-bromotoluene. Such a coupling reaction may be carried out similarly by use of Buchwald chemistry. For example, the 2-chloro-6-fluoroaniline and 4-bromotoluene are mixed with an organic base, e.g. sodium tertiary butylate in an organic solvent such as toluene; a palladium compound or catalyst precursor e.g. $Pd(dba)_2$, and a ligand, e.g. $P(tBu)_3$, or BINAP, are added to this reaction mixture which is then stirred at elevated temperature, e.g. 110°C, until completion of the reaction, e.g. overnight. Similarly the diphenylamine product of formula IV may be recovered from the organic phase of the reaction mixture, for instance after cooling and treatment with acid, e.g. HCl.

The compound of formula V is prepared by alkylation of 2-chloro-6-fluorophenol with 2-chloro-N-(4-methylphenyl)acetamide. For instance, 2-chloro-6-fluorophenol and 2-chloro-N-(4-methylphenyl)acetamide are mixed in an organic solvent such as 2-propanol in the presence of a base, e.g. K_2CO_3, and the reaction mixture boiled until completion of the reaction, e.g. for about 4 hours. The compound of formula V may be recovered from the reaction mixture if desired. Preferably, however, the compound of formula V is not isolated but is converted to the compound of formula IV, by rearrangement and hydrolysis as described above carried out on the product reaction mixture resulting from the alkylation of 2-chloro-6-fluorophenol with 2-chloro-N-(4-methylphenyl) acetamide.

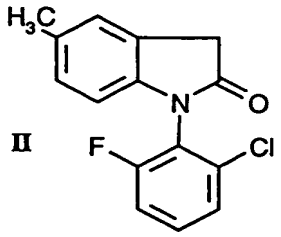
In starting compounds and intermediates, which are converted to the compounds of formulae I to VI in a manner as hereinbefore described, functional groups present such as amino, hydroxy and carboxyl groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected hydroxy, amino and carboxyl groups are those that can be converted under mild conditions into free amino, hydroxy and carboxyl groups without other

undesirable side reactions taking place. For example, hydroxy protecting groups are preferably benzyl or substituted benzyl groups.

The processes for the production of the compounds of formulae II, III, IV, V and VI, as described above, are novel processes and are included within the scope of the present invention.

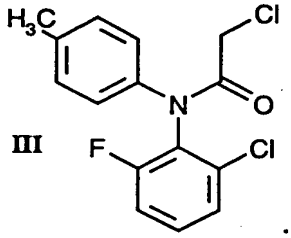
Thus in further aspects the invention includes

a) a process for the production of the oxindole lactam of formula II



II

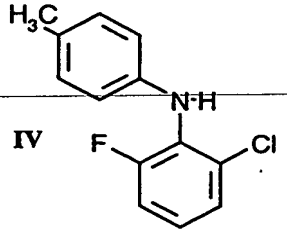
which comprises cyclisation of a compound of formula III



III

;

b) a process for the production of a compound of formula III which comprises N-acylation of a diphenylamine of formula IV (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine

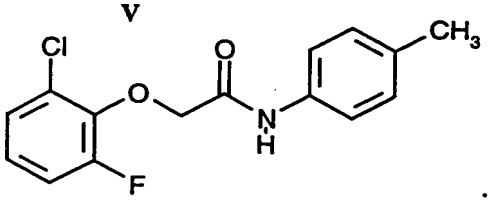


IV

with a haloacetyl chloride;

c) a process for the preparation of a compound of formula IV which comprises rearrangement and hydrolysis of a compound of formula V.

V



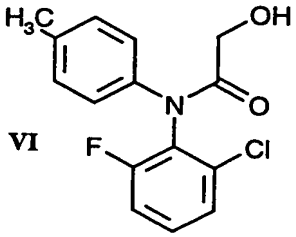
;

d) a process for the production of a compound of formula IV which comprises coupling of 2-bromo-1-chloro-3-fluorobenzene with p-toluidine;

e) a process for the production of a compound of formula IV which comprises coupling of 2-chloro-6-fluoroaniline with 4-bromotoluene;

f) a process for the production of a compound of formula IV which comprises hydrolysis of a compound of formula VI

VI



g) a process for the formation of a compound of formula VI which comprises rearrangement of a compound of formula V;

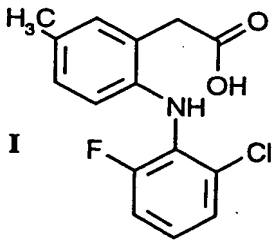
h) a process for the production of a compound of formula V which comprises alkylation of 2-chloro-6-fluorophenol with 2-chloro-N-(4-methylphenyl)acetamide; and

i) a process for the production of a compound of formula IV which comprises alkylation of 2-chloro-6-fluorophenol with 2-chloro-N-(4-methylphenyl)acetamide followed by rearrangement and hydrolysis of the intermediate compound of formula V.

One or more of the processes a) to i) above may be used in the preparation of the compound of formula I.

Thus the invention further provides a process for the preparation of a compound of formula I

I



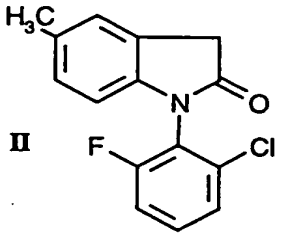
which comprises one or more of processes a) to i) as defined above.

Still yet further the invention provides a compound of formula I, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable prodrug ester thereof, when prepared by a process which comprises one or more of processes a) to i) as defined above.

The compounds of formulae II, III, IV, V and VI are novel compounds and are included per se within the scope of the present invention.

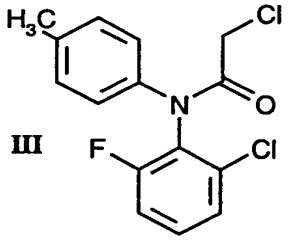
Thus in yet further aspects the invention provides:

a) a compound of formula II



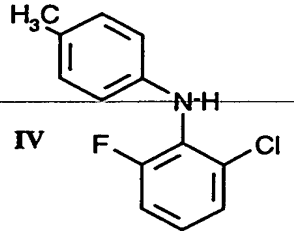
II

b) a compound of formula III



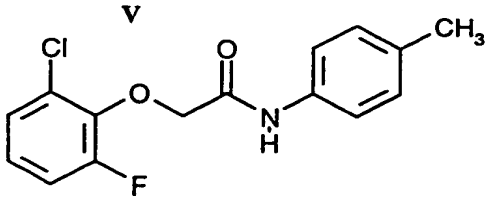
III

c) a compound of formula IV



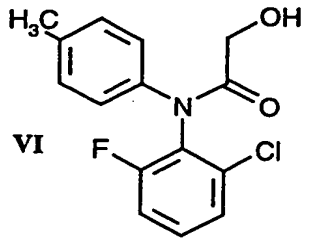
IV

d) a compound of formula V



and

e) a compound of formula VI



VI

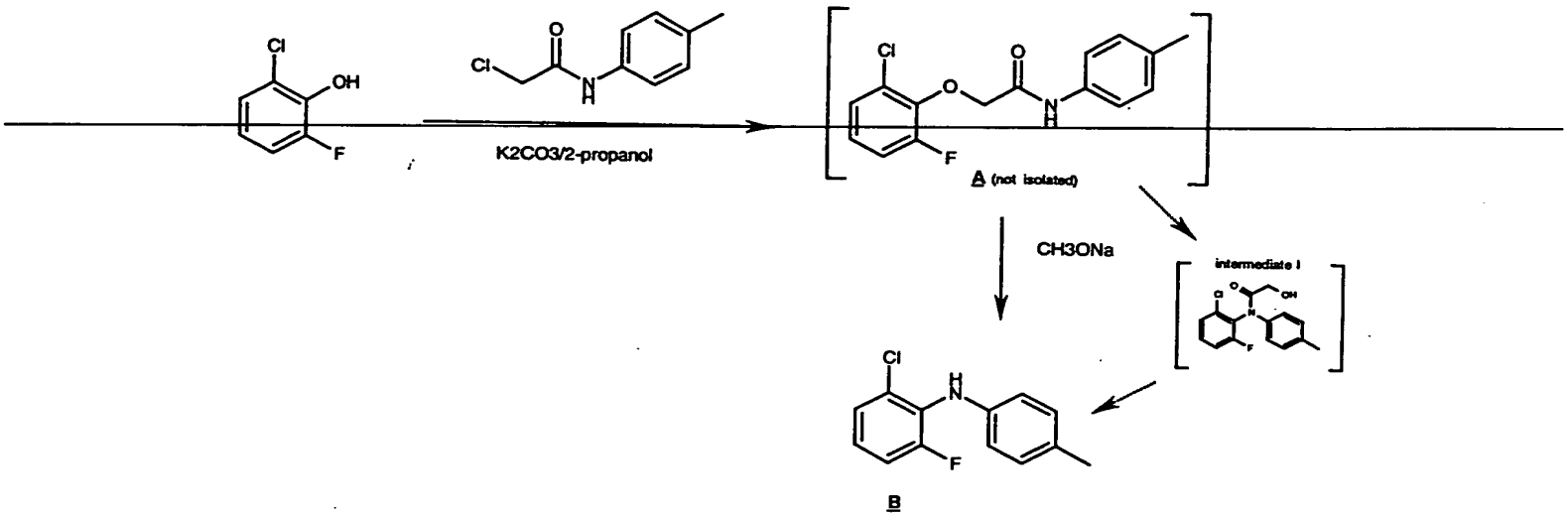
2-chloro-6-fluorophenol may be prepared by chlorination of 2-fluorophenol, preferably in the presence of catalytic amounts of a secondary amine, e.g. diisopropylamine. In a preferred embodiment according to the present invention, the chlorination reaction comprises simultaneous addition of chlorine and 2-fluorophenol to the reaction mixture, preferably using hexane fraction as the solvent. It has been found that simultaneous addition of at least part, preferably the majority, of the chlorine and 2-fluorophenol to the reaction mixture gives rise to high productivity and selectivity in production of the desired 2-chloro-6-fluorophenol product as compared with the unwanted 4-chloro and 2,4-dichloro side products. Furthermore use of hexane fractions permits isolation of the desired 2-chloro-6-fluorophenol product in high purity (e.g. 99%) by crystallisation.

Thus in a further aspect the invention provides a process for the production of 2-chloro-6-fluorophenol by chlorinationof 2-fluorophenol, which comprises simultaneous addition of chlorine and 2-fluorophenol to the reaction mixture, preferably using a solvent comprising hexane fraction.

The invention is further described by way of illustration only in the following Examples.

EXAMPLES

Example 1: **(2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine**



14.65 g (100 mmol) of 2-chloro-6-fluorophenol are dissolved in 50 ml of 2-propanol followed by the addition of 15.5 g (112 mmol) of potassium carbonate and 18.9 g (103 mmol) of 2-chloro-N-(4-methylphenyl)acetamide. The mixture is refluxed for 4h. At this time, the formation of A : 2-(2'-chloro-6'-fluorophenoxy)-N-(4-methylphenyl)acetamide is completed.

20 ml of sodium methylate solution 30% in methanol are slowly added. To maintain a temperature of at least 75°C, about 25 ml of solvent are distilled during the addition. The mixture is boiled 2h more to complete the formation of B.

Then 15 ml of solvent is distilled and 35 ml of water is added to obtain a two phases solution. The lower layer is discarded. The upper layer is diluted with 35 ml of heptane and washed with 3x 25 ml of water. The organic phase is separated and concentrated in vacuo to obtain 21.8 g of crude oil B: (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine. This compound (HPLC purity 92%) is used without purification in the next step.

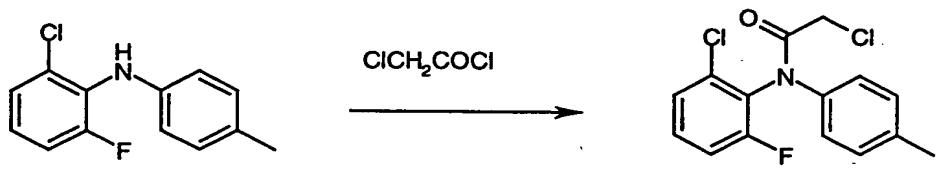
^{1}H-NMR (DMSO-d^6, 500 MHz, 300K) δ 2.17(s, 3H, CH_3); 6.53[dd, J = 8.5Hz, J_{H-F} = 1.5, 2H, HC(2) and HC(6)], 6.94[d, J = 8.0Hz, 2H, HC(3) and HC(5)],

7.16[ddd, J = 8.0Hz, J_{H-F} = 6.0, 1H, HC(4')], 7.25[ddd, J = 8.0,1.5Hz, J_{H-F} = 8.0, 1H, HC(5')]; 7.34[ddd, J = 8.0,1.5Hz, J_{H-F} = 1.5, 1H, HC(3')]; 7.63(s, 1H, NH).

MS(EI) m/z 235 (100, M^+), 200 (35, $(M-Cl)^+$), 185 (55)

Example 2.

2-chloro-N-(2'-chloro-6'-fluorophenyl)-N-(4-methylphenyl) acetamide



20.4 g of crude (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine are heated to about 80°C and treated with 10.75 g of chloroacetylchloride. The mixture is stirred for 2h and diluted with 10 ml of 2-propanol. The solution is cooled to 35-40°C and seeded. The precipitated suspension is diluted with 30 ml of hexane, cooled to 0-5°C and stirred for about 1h. The crystals are isolated by filtration, washed with a cold solution of 2-propanol/hexane 1/3. After drying, 22.7 g of 2-chloro-N-(2'-chloro-6'-fluorophenyl)-N-(4-methylphenyl)acetamide are obtained. HPLC purity: 99%. M.P.: 79-80°C.

^{1}H-NMR(DMF-d^7, 400 MHz, 393K) δ 2.44(s, 3H, CH_3); 4.32 (s, 2H, CH_2), 7.35[d, J = 8.0Hz, 2H, HC(3) and HC(5)], 7.43[ddd, J = 8.0,2.0Hz, J_{H-F} = 8.0 , 1H, HC(5')], 7.48[d, J = 8.0Hz, 2H, HC(2) and HC(6)], 7.55[d, J = 8.0Hz, 1H, HC(3')], 7.60[ddd, J = 8.0Hz, J_{H-F} = 5.5, 1H, HC(4')].

Preparation of starting material 2-chloro-6-fluorophenol

A solution of 12.1 g (108 mmol) of 2-fluorophenol, 70 mg of diisopropylamine and 400 ml of hexane-fraction is heated to 60-65°C.

4 g (56 mmol) of chlorine is introduced at this temperature. Then 60.5 g (540 mmol) of 2-fluorophenol are dropped in the solution over about 2h, while at the same rate 42g

(590 mmol) more chlorine is introduced. After that 4 g more chlorine are introduced to complete the chlorination.

GC check: 91% of 2-chloro-6-fluorophenol.

5.2% of 4-chloro-6-fluorophenol

3.5% of 2,4-dichloro-6-fluorophenol

200-250 ml of solvent are distilled at normal pressure. The resulting concentrated solution is slowly cooled to 0-5°C. The obtained thick suspension is stirred at this temperature for 1h, washed with cold hexane-fraction and dried at room temperature.

Yield: 78 g white crystals. GC 99.7%. M.P.: 63.5-64.5°C

MS(EI) m/z 146 (100, M^+), 126 [19, $(M-HF)^+$]

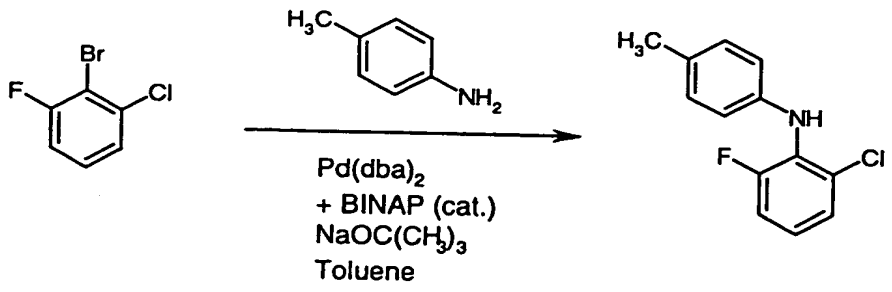
^{1}H-NMR(DMSO-d^6, 500MHz, 300K) δ 6.8[ddd, J = 8.2 Hz, J_{H-F} = 5.5, 1H, HC(4)], 7.15[m, 2H, HC(3) and HC(5)], 10.3(s, 1H, OH).

Preparation of starting material 2-chloro-N-(4-methylphenyl)acetamide

To a stirred mixture of 34.5 g (322 mmol) of p-toluidine, 100 ml of toluene and 100 ml of water are added at 20-25°C from two separated dropping funnels 42.3 g (375 mmol) of chloroacetylchloride and 39 ml of concentrated sodium hydroxide 30% at such a rate to maintain a pH of 8-12. The obtained suspension is cooled to 0-5°C. The crystalline compound is filtered, washed with water and cold toluene and dried.

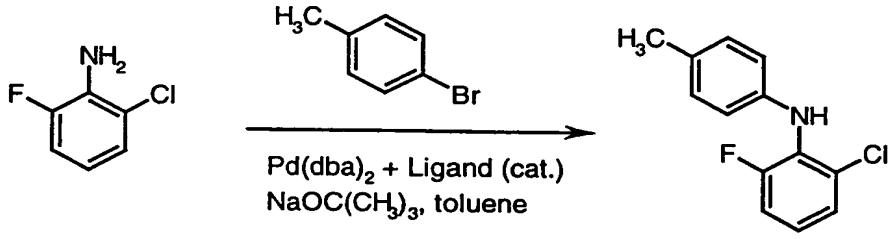
Yield: 55 g HPLC > 99%.

Example 3: (2'-Chloro-6'-fluorophenyl)-(4-methylphenyl)-amine from 2-bromo-1-chloro-3-fluorobenzene and p-toluidine.



A mixture of 2-bromo-1-chloro-3-fluorobenzene (32 g, 153 mmol), p-toluidine (16.4 g, 153 mmol), sodium tert.butylate (27.5 g, 286 mmol), (±)-BINAP [2,2'-Bis-(diphenylphosphino)-1,1'-binaphthalin, 0.66g, 1.1 mmol) and toluene (250 ml) is stirred under nitrogen for about 30 minutes. After the addition of Palladium-bis-(dibenzylidenaceton) (0.8 g, 1 mmol), the mixture is heated to 110°C (slight reflux) for 14-20 hours. The mixture is then cooled to 30°C, water (60 ml), concentrated hydrochloric acid (60 ml) as well as charcoal and cellite (5 g each) are added and stirring is continued for an hour. The mixture is filtered and the filtrate is separated into the phases. The organic phase is washed with water (3 times, 70 ml each) and concentrated in vacuo to obtain 37.2 g of crude (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine. The product can be used in the next step as such; alternatively in can be kugelrohrdistilled in vacuo.

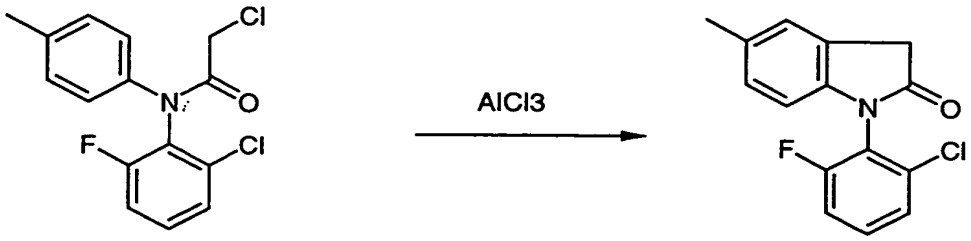
Example 4: (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine from 2-chloro-6-fluoroaniline and 4-bromotoluene.



A mixture of 2-chloro-6-fluoroaniline (4.00g, 27.5 mmol), 4-bromotoluene (4.70 g, 27.5 mmol), sodium *tert*-butylate (4.75 g, 49.4 mmol), and toluene (55 mL) is stirred at 25 °C under nitrogen for 30 minutes. To this mixture, a solution of palladium-bis-(dibenzylidenacetone) (15.8 mg, 55 mmol) and tri-*tert*-butylphosphine (1) (8.3 mg, 0.04 mmol) in toluene (5 mL) is added and the resulting suspension. is stirred at 110°C for 14 hours. The mixture is then cooled to 30°C. Water (30 ml), concentrated hydrochloric acid (10 ml), charcoal and cellite (1 g each) are added and stirring is continued for 1 hour. The mixture is filtered and the filtrate is separated into its phases. The organic phase is washed three times with water (10 mL) and

concentrated *in vacuo* to give 6.5 g of crude (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine. The product can be used directly in the next step. Alternatively, it can be distilled *in vacuo* by Kugelrohr.

Example 5: 1-(2'-Chloro-6'-fluorophenyl)-5-methyl-1,3-dihydro-indol-2-one

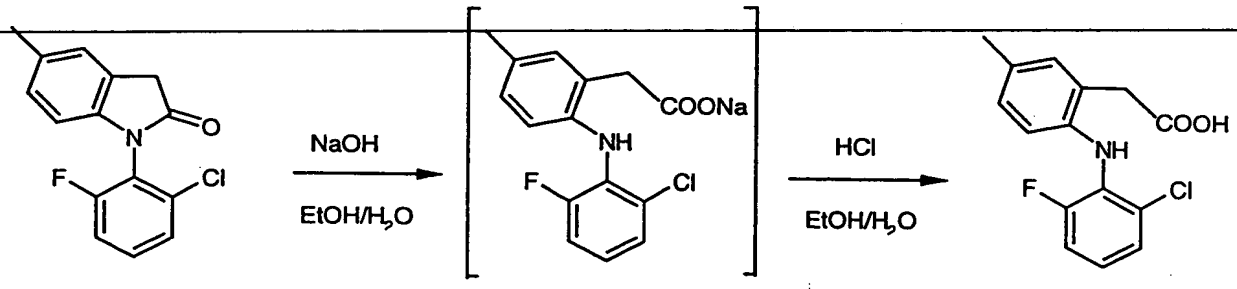


A melt of 124.8 g (400 mmol) of 2-chloro-N-(2'-chloro-6'-fluorophenyl)-N-(4-methylphenyl)acetamide at 100-120°C is treated with 69.3 g (520 mmol) of aluminium chloride in small parts. The mixture is heated to 160°C and stirred for 4-6h at this temperature.

The molten mixture is cooled to 110°C and diluted with 300 ml of toluene. The obtained solution is added to 500 ml of water at 60°C. The organic phase is separated while hot, decolorized with activated carbon, filtered and concentrated. The residue is dissolved in hot 2-propanol, decolorized again with activated carbon, filtered and concentrated to a volume of about 250 ml. The obtained suspension is cooled to 0-5°C, filtered, washed with cold 2-propanol. After drying, 87 g of 1-(2'-chloro-6'-fluorophenyl)-5-methyl-1,3-dihydro-indol-2-one are obtained. M.P.:137.5-138.5°C

^{1}H-NMR(DMSO-d^6, 500 MHz, 300K) δ 2.27(s, 3H, CH_3); 3.83(s, 2H, CH_2); 6.35[d, J = 8.0Hz, 1H, HC(7)], 7.01[d, J = 8.0Hz, 1H, HC(6)], 7.19[s, 1H, CH(4)], 7.52[ddd, J = 8.5,2.0Hz, J_{H-F} = 10.0, 1H, HC(5')], 7.60[ddd, J = 8.5,2.0Hz, J_{H-F} = 1.5, 1H, HC(3')], 7.63[ddd, J = 8.5Hz, J_{H-F} = 1.5, 1H, HC(4')].

Example 6. **[2-(2'-chloro-6'-fluoro-phenylamino)-5-methyl-phenyl]acetic acid**

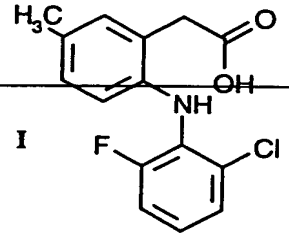


A mixture of 20 g of 1-(2'-chloro-6'-fluorophenyl)-5-methyl-1,3-dihydro-indol-2-one, 266 ml of ethanol and 11 ml of water is heated to reflux. 24 g of a 30% solution of sodium hydroxide is slowly added and reflux is continued for 1h. The solution is cooled to 40-45°C and treated slowly with a solution of 18 g of concentrated hydrochloric acid in 94 g of deionized water up to a pH of 3-4. The obtained suspension is cooled to 20-25°C and the crystalline material is collected by filtration, washed with ethanol/deionized water and dried under reduced pressure to yield 19.5 g of pure [2-(2'-chloro-6'-fluoro-phenylamino)-5-methyl-phenyl]acetic acid. M.P.: 152-154°C

^{1}H-NMR(DMSO-d^6, 500MHz, 300K) δ 2.21(s, 3H, CH_3), 3.64(s, 2H, CH_2); 6.42[dd, J = 8.0Hz, J_{H-F} = 3.0, 1H, HC(6)], 6.90[dd, J = 8.0,2.0Hz, 1H, HC(5)], 7.01[d, J = 2.0Hz, 1H, HC(3)], 7.09(s, 1H, NH), 7.09[ddd, J = 8.5Hz, J_{H-F} = 5.5, 1H, HC(4')], 7.23[ddd, J = 8.5,1.5Hz, J_{H-F} = 11.0, 1H, HC(5')], 7.34[ddd, J = 8.5,1.5Hz, J_{H-F} = 1.5, 1H, HC(3')], 12.67(s, 1H, COOH).

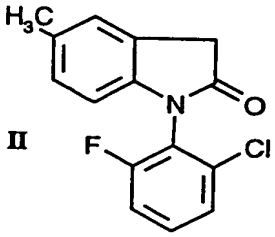
CLAIMS

1. process for the production of a compound of Formula I, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable prodrug ester thereof,



I

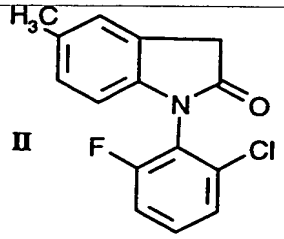
comprising hydrolysing a lactam of formula II



II

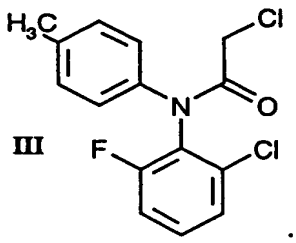
with a base; and in the above process, if desired, temporarily protecting any interfering reactive groups and then isolating the resulting compound of the invention; and, if desired, converting the free carboxylic acid of the compound of formula I into a pharmaceutically acceptable ester derivative thereof; and/or if desired, converting the free acid of formula I into a salt or a resulting salt into the free acid or into another salt.

2. a) a process for the production of the oxindole lactam of formula II



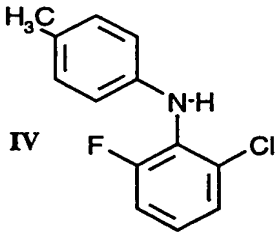
II

which comprises cyclisation of a compound of formula III



III ;

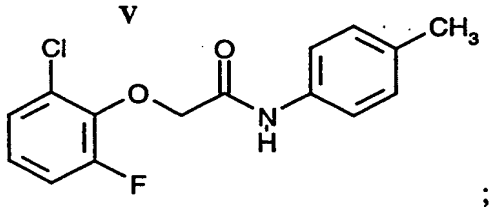
b) a process for the production of a compound of formula III which comprises N-acylation of a diphenylamine of formula IV (2'-chloro-6'-fluorophenyl)-(4-methylphenyl)-amine)



IV

with a haloacetyl chloride;

c) a process for the preparation of a compound of formula IV which comprises rearrangement and hydrolysis of a compound of formula V.

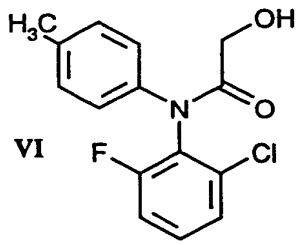


V ;

d) a process for the production of a compound of formula IV which comprises coupling of 2-bromo-1-chloro-3-fluorobenzene with p-toluidine;

e) a process for the production of a compound of formula IV which comprises coupling of 2-chloro-6-fluoroaniline with 4-bromotoluene;

f) a process for the production of a compound of formula IV which comprises hydrolysis of a compound of formula VI



VI

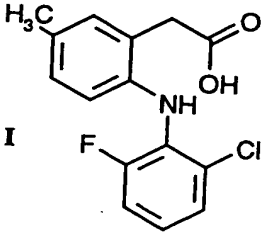
g) a process for the formation of a compound of formula VI

which comprises rearrangement of a compound of formula V;

h) a process for the production of a compound of formula V which comprises alkylation of 2-chloro-6-fluorophenol with 2-chloro-N-(4-methylphenyl)acetamide; or

i) a process for the production of a compound of formula IV which comprises alkylation of 2-chloro-6-fluorophenol with 2-chloro-N-(4-methylphenyl)acetamide followed by rearrangement and hydrolysis of the intermediate compound of formula V.

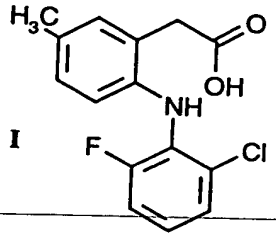
3. A process for the preparation of a compound of formula I



I

which comprises one or more of processes a) to i) as defined in claim 2.

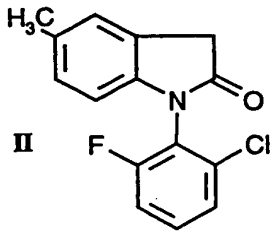
4. A compound of formula I,



I

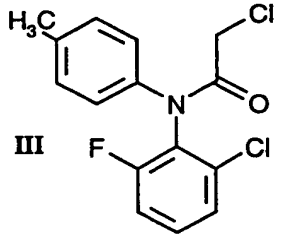
or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable prodrug ester thereof, when prepared by a process which comprises one or more of processes a) to i) as defined in claim 2.

5. a) a compound of formula II



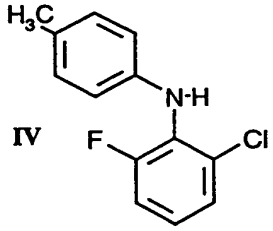
II

b) a compound of formula III



III

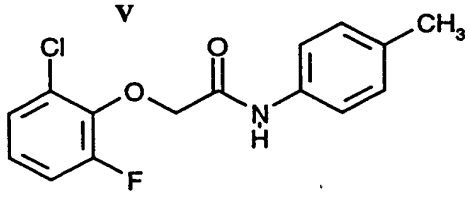
c) a compound of formula IV



IV

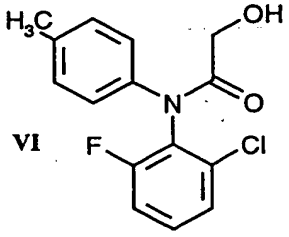
d) a compound of formula V

V



or

e) a compound of formula VI



VI

6. A process for the production of 2-chloro-6-fluorophenol by chlorination of 2-fluorophenol, which comprises simultaneous addition of chlorine and 2-

fluorophenol to the reaction mixture, preferably using a solvent comprising hexane fraction.

7. All novel products processes and utilities substantially as hereinbefore described, particularly with reference to the examples.